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Altered Functional Connectivity of the Default Mode Network in Patients With Schizo-obsessive Comorbidity: A Comparison Between Schizophrenia and Obsessive-compulsive Disorder

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Clinical and neuroimaging data support the idea that schizo-obsessive comorbidity (SOC), similar to obsessive-compulsive disorder (OCD) and schizophrenia (SCZ), may be a distinct brain disorder. In this study, we examined the strength of resting-state functional connectivity (rsFC) between 19 subregions of the default mode network (DMN) and whole brain voxels in 22 patients with SOC features, 20 patients with SCZ alone, 22 patients with OCD, and 22 healthy controls (HC). The main results demonstrated that patients with SOC exhibited the highest rsFC strength within subregions of the DMN and the lowest rsFC strength between the DMN and subregions of the salience network (SN) compared with the other 3 groups. In addition, compared with HCs, all 3 patient groups exhibited increased rsFC between subregions of the DMN and the executive control network (ECN). The SOC and SCZ group both exhibited increased rsFC between subregions of the DMN and the middle temporal gyrus, but the OCD group exhibited decreased rsFC between them. These findings highlight a specific alteration in functional connectivity in the DMN in patients with SOC, and provide new insights into the dysfunctional brain organization of different mental disorders.

Key words: schizo-obsessive comorbidity/schizophrenia/obsessive-compulsive disorder/functional connectivity/default mode network

Introduction

In 2013, the American Psychiatric Association (APA) officially released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which contained significant changes.[1] The main focus of these changes is that a dimensional classification (6 psychopathological dimensions: positive symptoms, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms, affection, and cognition) is recommended for the diagnosis of schizophrenia (SCZ).[2,3] This new framework conceptualizes SCZ as a psychotic spectrum disorder with a continuum of different deficits and evaluates independent and interrelated symptoms comprehensively.[4] A number of previous studies have confirmed the feasibility of this framework in the classification, diagnosis, and treatment of SCZ.[5–7] However, some other possible SCZ dimensions have been found in clinical studies, such as the "schizo-obsessive comorbidity (SOC)".[8,9] Comorbid obsessive-compulsive disorder (OCD) is diagnosed in 7.8%–26% of patients with SCZ,[9–13] approximately 10-fold higher than the incidence of OCD in the general population.[14] Patients with SOC features have been found to have an earlier age of onset and hospitalization,[15] more severe and complicated symptoms,[16] and more severe and longitudinally stable cognitive deficits compared with patients with SCZ or OCD

alone.[12] One study has reported a dual impact of OCD on functioning in SCZ with a gradual transition from an improving to a worsening effect depending on OCD symptoms severity.[17] Neuroimaging findings have shown that patients with SOC could have smaller whole brain gray matter volume,[18] smaller hippocampal volume,[19] and enlarged anterior horn of the lateral ventricles.[20] These results support the "double jeopardy hypothesis" of SOC.[21,22] However, whether SOC is a distinct subtype or subdimension of SCZ[23,24] remains controversial.

Aberrant functional integration within large-scale neuronal networks has been proposed as a core neural deficit of mental disorders.[25–27] Abnormal functional connectivity both within the component regions of the default mode network (DMN) and with other networks such as the salience network (SN) and the central executive network (CEN) have been reported in SCZ,[28] OCD,[29] autism,[30,31] major depressive disorder,[32,33] and post-traumatic stress disorder (PTSD).[34,35] The DMN is involved in many crucial cognitive functions associated with psychiatric symptoms including intrinsic stimulus-independent thoughts,[36] autobiographical memory, perspective-taking,[37] monitoring internal and external environment,[38] navigating social interactions,[39] consolidating past experience, adaptive pre-experience of upcoming events and constructing a unique, an integrated "self,"[40] and interacting with the SN and the ECN, in relation to self-monitoring and goal-directed behavior.[41] However, little is known about the changes in functional connectivity at the DMN in patients with SOC.

Since SOC is related to both SCZ and OCD, its underlying DMN functional alteration may show both similarities and differences with these 2 disorders. Some previous studies have shown that SCZ patients exhibited inappropriate over-activation within the DMN and decreased resting-state functional connectivity (rsFC) between the DMN and task-positive network such as the SN and the ECN,[42–45] while others have reported different patterns of rsFC within the DMN,[46] and between the DMN and other networks.[40] Moreover, reduced rsFC strength within the DMN,[47,48] and increased rsFC strength between the DMN and sub-regions of the SN and the ECN[29,49,50] have been reported in patients with OCD.

In addition, investigating the rsFC between subregions of the DMN and whole brain voxels and its correlation with different symptoms in patients with SOC could identify the similarity and difference in functional networks between patients with SOC and patients with either SCZ or OCD, and could clarify the relationship between symptom dimensions and brain dysfunction.

In this study, we aimed to compare the rsFC changes between DMN subregions and whole brain voxels in patients with SOC, SCZ, OCD, and healthy controls (HCs) using resting-state functional magnetic resonance imaging (fMRI). Since the majority of previous studies in patients with SCZ showed increased rsFC within the DMN and the influence of SCZ symptoms on brain function generally is more severe and extensive than OCD symptoms,[42–45,51] we hypothesized that patients with SOC would show similar but more severe symptoms and rsFC changes within the DMN than patients with either SCZ or OCD.

Materials and Methods

Participants

Twenty-two patients with SOC, 20 SCZ patients, and 22 OCD patients in remission were recruited from the Department of Psychiatry, the Second Xiangya Hospital of the Central South University in Changsha, Hunan, China. Twenty-two healthy participants were recruited as controls from the local community. Consensus diagnoses of the patients were ascertained by 2 experienced psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorder, Patient Edition (SCID-IV).[52] Patients with SOC met the diagnostic criteria of SCZ and OCD simultaneously, while SCZ and OCD patients met the diagnostic criteria of SCZ and OCD, respectively. HCs were screened using the nonpatient edition of the SCID-IV to confirm the absence of psychiatric disorders. In addition, individuals with any family history of psychiatric disorder were excluded.

The exclusion criteria for all participants were a history of nicotine, alcohol, or substance dependence, craniocerebral trauma, serious physical illness, or neurological disorders; an intelligence quotient (IQ) of less than 70; and contraindications for MRI scanning such as pregnancy, claustrophobia, and having metal dentures, prostheses, or pacemakers in the body. Participants who were uncooperative, whose head motions were greater than 2 mm displacement and/or 2° rotation in the x, y, or z axes throughout the course of the scans were also excluded.

The study protocol was designed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Xiangya Hospital of the Central South University, Changsha, China. All participants provided written informed consent.

Instruments

The symptoms of SCZ were rated by trained clinicians using the Positive and Negative Syndrome Scale (PANSS), which consists of the positive, negative, and general psychopathology subscales.[53] Obsessive-compulsive symptoms were measured using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS), which consists of the obsessive thought and compulsive behavior subscales.[54] The IQ of participants were estimated with the short-form of the Chinese version of the Wechsler Adult Intelligence Scale—Revised[55] using the "common sense," "arithmetic," "similarity," and "digital span" subtests.

Scanning Acquisition

All imaging data were acquired using a Siemens SKYRA 3.0T MR scanner (Siemens Medical) at the Second Xiangya Hospital of the Central South University, Changsha, China. Resting-state fMRI data were acquired using a T2-weighted echo planar imaging (EPI) sequence; 200 whole-brain volumes were collected with slices = 39, slice thickness = 3.5 mm, echo time (TE) = 25 ms, repetition time (TR) = 2500 ms, flip angle = 90°, matrix size = 64 × 64, field of view (FOV) = 200 mm, voxel size = 3.1 × 3.1 × 3.5 mm^3.

High-resolution T1-weighted anatomical images were obtained with a magnetization prepared rapid gradient echo (MPRAGE) sequence, with the following parameters: repetition time (TR) = 1900 ms, echo time (TE) = 2.01 ms, inversion time = 900 ms, field of view (FOV) = 256 mm, flip angle = 9°, in-plane matrix resolution = 256 × 256, slice thickness = 1 mm, slices = 176, and voxel size = 1 × 1 × 1 mm^3.

During scanning, the participants were instructed to remain awake with their eyes closed. The images were screened by a radiologist to exclude any incidental clinical abnormalities before further analysis.

Data Preprocessing

Participants' data were preprocessed by the Statistical Parametric Mapping Software (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing & Analysis for Brain Imaging (DPABI2.1, http://www.rfmri.org/dpabi) Software[56] in MATLAB R2014b (MathWorks, Inc.). The first 10 volumes at the beginning of the resting state scan were discarded to ensure steady-state magnetization. Secondly, slice timing and head motion correction were performed to correct slice order and head motion effects, and a mean functional image was obtained for each participant. Thirdly, the participants' structural images were manually co-registered and realigned with the anterior commissure-posterior commissure line, and subsequently co-registered to the mean functional image, and segmented as gray matter, white matter, and cerebrospinal fluid.[57] Fourthly, each functional image was normalized to the standard Montreal Neurological Institute space in 3 × 3 × 3 mm^3 voxel sizes with the application of the parameters obtained during segmentation. Fifthly, spatial smoothing was performed with an 8 mm full-width at half maximum. Subsequently, the linear trends were removed. Finally, the images were temporally band-pass filtered (0.01–0.1 Hz) to reduce low-frequency drift and high-frequency noise. The nuisance covariates, including head motion parameters, white-matter signal and cerebrospinal fluid signal were regressed out. The global signal was not regressed out because doing so may introduce artefactual negative correlations in rsFC analysis.[58]

To exclude artefacts caused by head motion, we took the Friston 24-parameter model as a regressor for the first-level analysis,[59] which has been shown to be superior to the 6-parameter model.[60] We also calculated the mean frame-wise displacement (FD)[61] of each participant and took it as a covariate in the second-level analysis as suggested by Yan.[60]

Functional Connectivity Analysis

The DMN was identified using a publicly available atlas of functionally defined regions of interests (ROIs), developed by the Functional Imaging in Neuropsychiatric Disorders (FIND) lab at Stanford University, downloaded at http://findlab.stanford.edu/functional_ROIs.html. This includes 19 subregions, from dorsal region 1 (D1) to dorsal region 9 (D9) and ventral region 1 (V1) to ventral region 10 (V10), mainly including the medial frontal gyrus (medial FG), the posterior cingulate cortex (pCC), the precuneus, the thalamus, the fusiform gyrus, the angular gyrus, the hippocampus, and the right cerebellum 9 region (see supplementary table S1 and supplementary figure S1 of Appendix).[62]

To examine whether the functional connectivity of the DMN was altered in different disorders, 19 subregions of the DMN were used as ROIs to compute the voxel-wise rsFC analysis between the seeds and other voxels in the whole brain by DPABI. Firstly, the mean time series of the seeds were calculated and correlated with the time series of all other whole brain voxels. The correlation maps produced in this analysis were then converted to Z-maps using Fisher's r-to-z transformation. Full factorial model was conducted to identify the regions that had significant rsFC difference within the 19 seeds among the 4 groups by SPM12 in the general linear model. In addition, according to previous studies showing the influence of age, gender, IQ, and mean FD on brain functional connectivity,[50,60,63] these 4 factors were entered as covariates in the analysis. The clusters were considered significant if they reached a threshold of $P < .001$ with alpha-sim 0.05 correction (cluster size > 41 voxels), calculated using DPABI.[56] The DMN, the SN, and the ECN templates developed by the FIND lab were used to verify whether the rsFC results belonged to specific brain networks. The SN mainly included the fronto-insular cortex, the supplementary motor area (SMA), the anterior cingulate cortex (aCC), the parietal cortex, and the cerebellum 6 region.[62] The ECN included the dorsolateral prefrontal cortex (DLPFC), the angular gyrus, the parietal cortex, the occipital cortex, and the cerebellum crus 2 region.[64] The images were visualized with BrainNet Viewer.[65]

To test whether rsFC differences were correlated with the corresponding clinical symptoms in patients with SOC, the significantly different rsFC results between patients with SOC and HCs were selected as ROIs. The rsFC values of these ROIs were extracted by REST (http://www.restfmri.net) and partial correlation analysis was conducted with scores on the positive, negative, and

general psychopathology subscales of the PANSS, as well as scores on the Y-BOCS obsessive thinking and compulsive behavior subscales, with age, gender, IQ, and mean FD entered as covariates. The significance level was set at $P < .05$.[66]

To investigate whether rsFC differences were correlated with disease dimensions across the diagnostic categories, we also conducted correlation analysis between the subscale scores of the PANSS and the whole brain rsFC of DMN subregions in the combined SOC and SCZ group, between the subscale scores of Y-BOCS and the whole brain rsFC of DMN subregions in the combined SOC and OCD group ($P < .001$, cluster size > 41 voxels).

Results

Demographics

There was no significant difference between the four groups in gender, age, mean FD, and PANSS and Y-BOCS compulsive behavior subscale scores. There was a significant difference in the Y-BOCS obsessive thinking subscale scores between the SOC group and the OCD group (mean difference = 2.29, $P < .05$). The 4 groups were also significantly different in estimated IQ ($F = 13.66$, $df = 3$, $P < .01$). Post hoc analyses with Bonferroni correction showed that the HC group had significantly higher estimated IQ than the other 3 groups (mean difference with SOC = 24.86, $P < .01$; mean difference with SCZ = 22.20, $P < .01$; mean difference with OCD = 12.09, $P < .05$), and the mean estimated IQ of OCD patients was significantly higher than patients with SOC (mean difference = 12.77, $P < .05$) (table 1).

Functional Connectivity Within the DMN

The results of the full-factorial model analysis showed that patients with SOC exhibited significantly increased rsFC strength within the DMN subregions relative to the other 3 groups. In comparison with HCs, SCZ patients especially exhibited increased rsFC between the thalamus and the left precuneus, between the right hippocampus (Hippo) and the right angular gyrus, between the left fusiform and the medial orbital frontal gyrus (medial oFG), between the right fusiform and the thalamus, and between the right mOG and the left smFG (table 2 and figure 1).

In addition, the rsFC between the thalamus and the left precuneus correlated positively with the Y-BOCS obsessive thinking subscale scores ($r = .59$, $P = .01$) and the Y-BOCS compulsive behavior subscale scores ($r = .57$, $P = .01$). The rsFC between the left fusiform and the medial oFG correlated inversely with Y-BOCS compulsive behavior subscale scores ($r = -.58$, $P = .01$) in patients with SOC.

Functional Connectivity Between the DMN and Other Networks

Patients with SOC exhibited decreased rsFC strength between the DMN and the SN compared with the other groups, which was mainly found between the DMN subregions and the SMA.

The rsFC between the DMN and the ECN was significantly increased in patients with SOC, compared with HCs, especially between the DMN subregions and the inferior triangular frontal gyrus (itFG). The rsFC between the medial frontal gyrus (medial FG) and the left itFG

Table 1. Demographic and Psychopathological Data of Patients and HC Subjects

	SOC ($n = 22$)	SCZ ($n = 20$)	OCD ($n = 22$)	HCs ($n = 22$)	$F/\chi^2/t$	P
Gender (M/F)	14/8	12/8	11/11	11/11	*1.29*	*0.73*
Age (years)	22.00 (4.83) (17–36)	21.50 (3.95) (16–30)	22.41 (6.21) (16–34)	22.68 (2.30) (17–27)	*0.27*	*0.88*
IQ	96.59 (15.26) (79–124)	99.25 (14.87) (79–130)	109.36 (15.87) (80–136)	121.45 (10.31) (97–138)	*13.66*	*0.001***
Mean FD	0.07 (0.02) (0.04–0.11)	0.07 (0.03) (0.03–0.14)	0.09 (0.05) (0.04–0.22)	0.07 (0.03) (0.04–0.15)	2.76	0.05
PANSS positive symptoms	14.36 (5.06) (7–22)	16.20 (4.23) (11–25)	NA	NA	*-1.27*	*0.21*
PANSS negative symptoms	9.09 (3.02) (7–20)	8.85 (2.39) (7–15)	NA	NA	*0.29*	*0.78*
PANSS general psychopathology	29.18 (6.71) (18–43)	30.70 (6.44) (19–43)	NA	NA	*-0.75*	*0.46*
Y-BOCS obsessive thinking	16.91 (2.97) (11–22)	NA	14.50 (3.95) (8–20)	NA	*2.29*	*0.03**
Y-BOCS compulsive behavior	12.68 (4.87) (5–20)	NA	12.68 (3.77) (5–22)	NA	*0.00*	*1.00*

Note: OCD, obsessive-compulsive disorder; SCZ, schizophrenia; SOC, schizo-obsessive comorbidity; HCs, healthy controls; IQ, intelligence quotient; FD, frame-wise displacement of head movement; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; Y-BOCS, Yale–Brown Obsessive Compulsive Scale; *$P < 0.05$ was considered significant; **$P < 0.01$. Data are presented as means (standard deviation) (range).

Table 2. Notable Groups Differences of the rsFC Between DMN Subregions and Whole Brain Voxels in 4 Groups Using Post Hoc in Full-factorial Model Analysis ($P < .001$, Cluster Size > 41 Voxels)

DMN	Region	Peak MNI coordinates			Voxels	*T*
		X	*Y*	*Z*		
A. SOC vs HCs						
D1 (L&R medial FG)	L itFG	−48	21	21	53	3.88
	R SMA	9	15	57	58	−4.68
D6 (R angular)	L iTG	−36	3	−42	42	5.30
D7 (L&R thalamus)	R itFG	51	33	0	95	5.43
	L precuneus	−15	−66	60	67	4.23
	vermis 4	0	−57	−9	76	−4.80
D9 (R Hippo)	R angular	42	−69	39	44	3.82
V3 (L fusiform)	L&R medial oFG	9	54	−9	120	4.67
	L&R SMA	6	3	54	45	−3.97
V8 (R fusiform)	L&R thalamus	−3	−18	6	56	4.64
V9 (R mOG)	L&R smFG	−3	60	36	53	4.18
V10 (R cerebellum 9)	R mTG	66	−51	12	63	4.71
B. SOC vs SCZ						
D1 (L&R medial FG)	R sTG	57	−12	−9	85	4.45
	L ioFG	−57	12	3	63	−4.14
	L mFG	−27	39	30	101	−4.73
	R sFG	24	54	12	108	−4.82
D3 (R sFG)	R sFG	27	63	12	123	−3.97
	L mFG	−27	39	30	48	−4.28
D4 (L&R pCC)	R insula	39	9	0	52	−4.33
	R sFG	24	48	12	65	−3.94
D6 (R angular)	R ParaHippo	30	−18	−18	45	3.99
D7 (L&R thalamus)	L sFG	−12	39	36	88	4.48
	L mFG	−24	−9	51	51	4.01
D8 (L Hippo)	R putamen	24	0	6	44	−4.58
D9 (R Hippo)	L&R medial oFG	0	45	−18	44	3.63
	L pCC	−6	−48	21	52	3.68
	L cerebellum 6	−24	−63	−30	60	−4.24
V1 (L calcarine)	R insula	39	6	0	43	−3.91
V2 (L mFG)	L sTG	−48	−36	15	53	−4.11
V3 (L fusiform)	L medial oFG	−3	63	−3	76	4.12
	R insula	33	12	3	93	−4.44
	R putamen	24	3	6	64	−4.44
	L ioFG	−48	9	0	97	−4.03
	R sTG	51	−21	21	156	−4.11
V4 (L mOG)	R insula	48	3	3	61	−3.90
V5 (R precuneus)	R ParaHippo	33	−30	−12	45	4.30
	R insula	42	6	−6	75	−4.48
	R mFG	30	45	15	40	−4.12
V7 (R mFG)	R cerebellum crus2	36	−84	−45	46	4.29
	R sTG	57	12	−3	112	−4.30
	L precentral	−45	−6	42	48	−3.97
	L SMA	−9	0	57	46	−4.45
C. SOC vs OCD						
D1 (L&R medial FG)	L mTG	−54	−54	0	55	−4.28
	L postcentral	−30	−39	63	156	−3.90
D3 (R sFG)	R SMA	15	6	66	80	−4.72
D4 (L&R pCC)	R ParaHippo	24	−18	−18	42	4.00
	R SMA	15	9	60	57	−4.10
D5 (L&R mCC)	L precentral	−33	−12	39	51	−4.08
	R precentral	39	−6	36	55	−4.75
D6 (R angular)	R SMA	9	0	72	66	−4.27
D7 (L&R thalamus)	R sTG	48	9	−21	81	4.88
	Vermis 4	0	−57	−9	165	−5.30
D8 (L Hippo)	L&R precuneus	6	−54	27	74	3.63
D9 (R Hippo)	L&R Precuneus	−3	−51	18	135	4.48
	L&R pCC	−3	−48	27	59	3.41
	L angular	−33	−75	48	83	3.89
	Vermis 7	3	−69	−30	61	−4.03
	L&R SMA	6	0	60	170	−4.84

Table 2. *Continued*

DMN	Region	Peak MNI coordinates			Voxels	*T*
		X	*Y*	*Z*		
V3 (L fusiform)	L&R precuneus	−3	−54	12	92	3.85
	L angular	−30	−69	42	56	3.89
V4 (L mOG)	L&R SMA	3	6	51	49	−3.95
V7 (R mFG)	L sFG	−21	−3	54	60	−4.04
	R sFG	27	−3	54	46	−3.91
V9 (R mOG)	R SMA	12	3	69	61	−4.05

Note: rsFC, resting-state functional connectivity; DMN, default mode network; MNI, Montreal Neurological Institute; SOC, schizo-obsessive comorbidity; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; HCs, healthy controls; sFG, superior frontal gyrus; mFG, middle frontal gyrus; soFG, superior forntal gyrus, orbital part; smFG, superior medial frontal gyrus; itFG, inferior frontal gyrus, triangular part; ioFG, inferior frontal gyrus, opercular part; medial FG, medial frontal gyrus; medial oFG, medial orbital frontal gyrus; mCC, middle cingulate cortex; pCC, posterior cingulate cortex; SMA, supplementary motor area; sTG, superior temporal gyrus; mTG, middle temporal gyrus; iTG, inferior temporal gyrus; sPL, superior parietal lobule; mOG, middle occipital gyrus; Hippo, hippocampal gyrus; ParaHippo, parahippocampal gyrus; L, left; R, right.

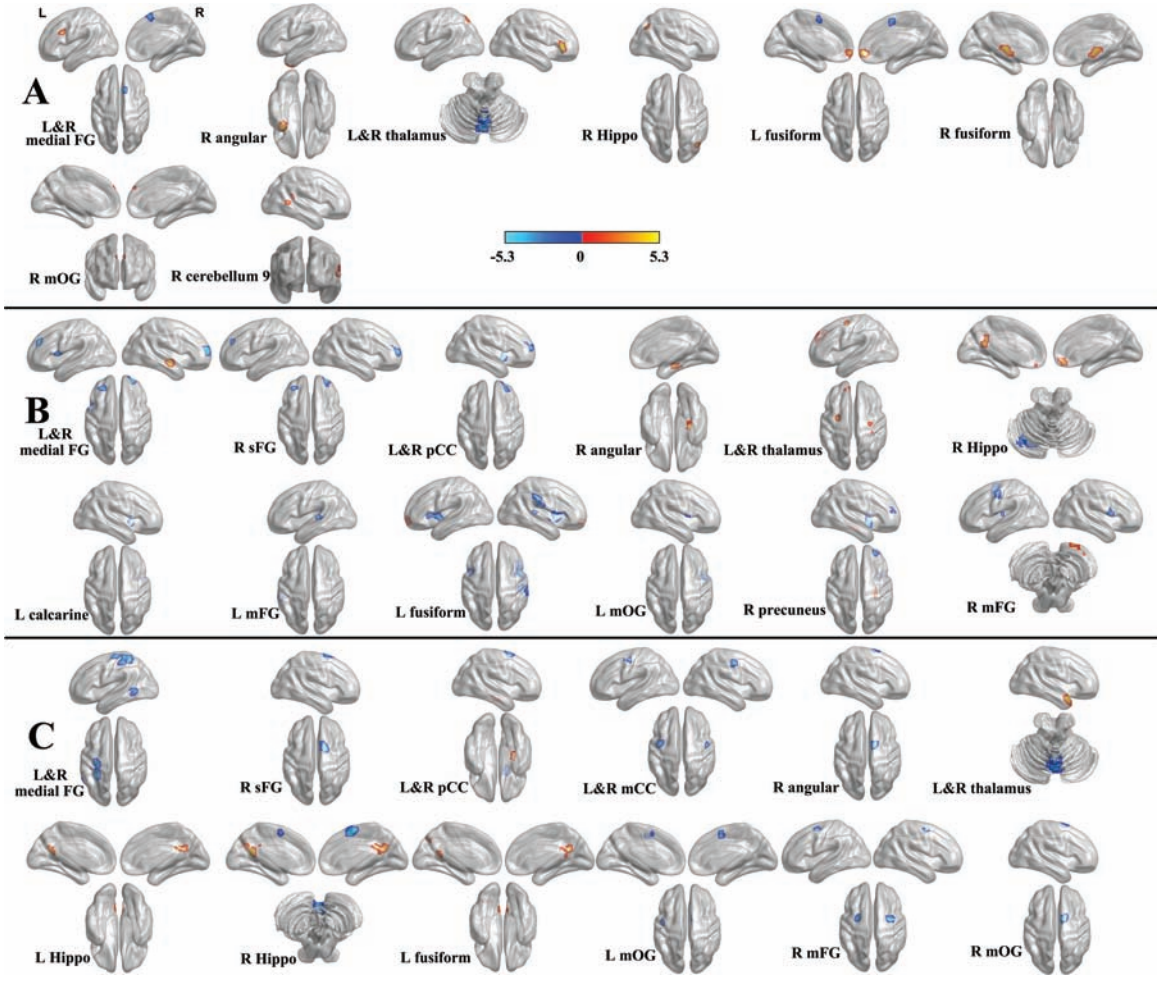

Fig. 1. Notable group differences in rsFC between DMN subregions (as seen at the lower left sub-graph) and whole brain voxels in the 4 groups using full-factorial model analysis ($P < .001$, cluster size > 41 voxels). (A) SOC vs HCs. (B) SOC vs SCZ. (C) SOC vs OCD. SOC, schizo-obsessive comorbidity; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; HCs, healthy controls; rsFC, resting-state functional connectivity; DMN, default mode network; medial FG, medial frontal gyrus; sFG, superior frontal gyrus; mFG, middle frontal gyrus; mOG, middle occipital gyrus; mCC, middle cingulate cortex; pCC, posterior cingulate cortex; Hippo, hippocampal gyrus.

correlated positively with Y-BOCS compulsive behavior subscale scores ($r = .51$, $P < .05$) in patients with SOC.

We also observed increased rsFC between the DMN and the mTG, which does not belong to either the SN or the ECN in the SOC and SCZ group, compared with HCs (table 2 and figure 1). The OCD patients showed decreased rsFC between them.

In addition, compared with the HC group, SCZ patients exhibited increased rsFC within the DMN subregions, decreased rsFC between the DMN and the SN subregions, increased rsFC between the DMN and the ECN subregions including the middle orbital frontal gyrus (moFG), the right itFG; and decreased rsFC between the DMN and the ECN sub-regions including the left middle frontal gyrus (mFG) and the right superior parietal lobule (sPL). OCD patients showed decreased rsFC within the DMN subregions, and increased rsFC between the DMN and both the SN and the ECN (see supplementary table S2 and supplementary figure S2 of Appendix).

Correlation Between PANSS and Y-BOCS Subscale Scores and DMN Functional Connectivity

In the combined SOC and SCZ group, the PANSS positive subscale scores correlated positively with the rsFC between DMN subregions and the left precentral gyrus and the right iTG. They also correlated inversely with the rsFC between DMN subregions and the aCC and the left mTG. The PANSS negative subscale scores correlated positively with the rsFC between DMN subregions and the right mFG. The PANSS general psychopathology subscale scores correlated inversely with the rsFC within the DMN and between the DMN subregions and the temporal gyrus.

In the combined SOC and OCD group, the Y-BOCS obsessive thinking subscale scores correlated positively with the rsFC within the DMN and between DMN subregions and ECN subregions and the right cuneus. They also correlated inversely with the rsFC between DMN subregions and the left sTG. The Y-BOCS compulsive behavior subscale scores correlated positively with the rsFC between DMN subregions and SN subregions, the right precentral gyrus, the cerebellum, the right cuneus, and the left lingual gyrus. They also correlated inversely with the rsFC within the DMN and between DMN subregions and the caudate (table 3 and figure 2).

Discussion

In this study, we compared the rsFC changes between DMN subregions and whole brain voxels in patients with SOC, patients with SCZ, patients with OCD, and HCs. We also investigated the relationship between PANSS and Y-BOCS scores and the rsFC of the DMN in patients. Although all patients were in remission and there was no significant clinical difference between patients with SOC and the other patient groups except the Y-BOCS obsessive thinking subscale scores and estimated IQ, our results support the hypothesis that patients with SOC showed increased rsFC within the DMN subregions and decreased rsFC between the DMN and the SN compared with the other 3 groups. We also found significantly increased rsFC between the DMN and the ECN in the SOC group compared with HCs.

Increased rsFC within the DMN has often been reported in studies of SCZ patients and has been associated with impaired self-related mental simulation, self-regulation deficits,[67] chaotic autobiographical memory, unintegrated emotion and behavior,[68] and inability in distinguishing thoughts and real perceptions.[43] All of these may be closely related to perceptual disturbances and may contribute to typical SCZ symptoms such as hallucinations, delusions, and behavioral disturbance.[67,69] The increased rsFC within the DMN in patients with SOC compared with the other diagnostic groups may be the neural substrate underlying impaired cognitive functions on the one hand, and strengthened preferential memory of pathological thinking and behavior on the other hand, associated with the co-expression of both SCZ and OCD symptoms.

In addition, we found that the rsFC between the thalamus and the left precuneus correlated positively with the Y-BOCS obsessive thinking subscale scores and Y-BOCS compulsive behavior subscale scores in patients with SOC. The thalamus has been shown to be involved in reward expectation, attention, emotion, memory,[70] and executive function.[71] The precuneus is involved in visuospatial imagery, episodic memory retrieval, and self-centered mental imagery strategies.[72] Our finding suggests that abnormal thalamic-precuneus connectivity may be a neuroimaging marker of the cumulative cognitive decline and neural abnormality of obsessive-compulsive symptoms in SCZ patients.[73] The rsFC between the left fusiform gyrus and the medial oFG correlated inversely with Y-BOCS compulsive behavior subscale scores in patients with SOC, suggesting that obsessive behavior may be a reflection of neural adaptation, ie, a compensatory effect in patients with SOC.[17] A similar mechanism has been found in generalized anxiety disorder and PTSD patients.[74]

Another important observation in this study is that patients with SOC exhibited significantly decreased rsFC between the DMN and the SN, particularly between DMN subregions and the SMA. The major functions of the SN are vigilance, orientation, execution,[46] and integrating salient external stimuli and internal events.[40] Previous studies in patients with SCZ have also reported decreased rsFC between the DMN and the SN.[42,46] Decreased rsFC between the DMN and the SN in patients with SOC may imply the existence of a chaotic relationship between internal perception and external environmental surveillance and behavior, which may be associated with psychiatric symptoms and behavioral disturbances simultaneously.[75–78] However, increased rsFC between the DMN and the SN was also found in the OCD group,

Table 3. Notable Correlation Between the Questionnaire Subscale Scores and the Whole Brain rsFC of DMN Subregions ($P < .001$, Cluster Size > 41 Voxels)

DMN	Region	Peak MNI coordinates			Voxels	*r*
		X	*Y*	*Z*		
A. PANSS positive scores (SOC + SCZ group)						
D6 (R angular)	L&R aCC	*0*	*30*	*−6*	*77*	−4.96
D8 (L Hippo)	L precentral	*−60*	*0*	*24*	51	4.64
V6 (L&R precuneus)	L mTG	*−48*	*−48*	*9*	*53*	−5.41
V9 (R mOG)	R iTG	*45*	*−39*	*−12*	*47*	6.20
	L&R aCC	*6*	*30*	*−3*	*44*	−4.54
B. PANSS negative scores (SOC + SCZ group)						
V1 (L calcarine)	R mFG	*27*	*39*	*27*	*43*	*4.23*
V9 (R mOG)	R mFG	*21*	*39*	*21*	*41*	*4.03*
C. PANSS general scores (SOC + SCZ group)						
V9 (R mOG)	L&R smFG	*0*	*66*	*6*	*81*	*−5.27*
	L mTG	*−45*	*−69*	*21*	*69*	*−4.88*
	R mTG	*45*	*3*	*−27*	*47*	*−4.59*
	L sTG	*−33*	*18*	*−30*	*49*	*−4.65*
D. Y-BOCS obsessive thinking scores (SOC + OCD group)						
D1 (L&R medial FG)	R cuneus	*18*	*−99*	*12*	*79*	*4.51*
D4 (L&R pCC)	L cerebellum crus1	*−3*	*−93*	*−21*	*59*	*4.59*
V1 (L calcarine)	L&R precuneus	*3*	*−69*	*54*	*72*	*4.59*
V10 (R Cerebellum 9)	L sTG	*−39*	*12*	*−24*	*44*	*−4.27*
E. Y-BOCS compulsive behaviour scores (SOC + OCD group)						
D1 (L&R medial FG)	R fusiform	*30*	*−33*	*−24*	*94*	*−5.61*
	L pCC	*−9*	*−45*	*24*	*308*	*−4.74*
D2 (L angular)	R precentral	*60*	*−3*	*39*	*50*	*5.21*
D4 (L&R pCC)	L&R smFG	*6*	*54*	*36*	*128*	*−4.49*
D5 (L&R mCC)	Vermis 8	*3*	*−57*	*−36*	*191*	*6.38*
	L&R smFG	*−15*	*48*	*15*	*309*	*−5.07*
D9 (R Hippo)	L&R caudate	*−3*	*15*	*−3*	*110*	*−5.14*
V1 (L calcarine)	R cerebellum 8	*33*	*−48*	*−48*	*119*	*4.84*
	R medial oFG	*6*	*18*	*−6*	*46*	*−4.15*
	L&R smFG	*−12*	*51*	*18*	*513*	*−5.57*
V2 (L mFG)	L insula	*−30*	*−33*	*18*	*49*	*4.55*
V4 (L mOG)	L cerebellum 6	*−30*	*−60*	*−27*	*107*	*5.68*
	L lingual	*−15*	*−96*	*−15*	*81*	*4.26*
V5 (R precuneus)	L&R smFG	*−12*	*54*	*15*	*323*	*−5.34*
V7 (R mFG)	L&R aCC	*−6*	*21*	*12*	*66*	*−4.59*
V8 (R fusiform)	R cuneus	*12*	*−69*	*36*	*58*	*4.84*
	L sFG	*−18*	*36*	*39*	*45*	*−4.79*
	L&R medial oFG	*3*	*18*	*−15*	*764*	*−5.40*

Note: rsFC, resting-state functional connectivity; DMN, default mode network; MNI, Montreal Neurological Institute; SOC, schizo-obsessive comorbidity; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; PANSS, Positive and Negative Syndrome Scale; Y-BOCS, Yale–Brown Obsessive Compulsive Scale; sFG, superior frontal gyrus; mFG, middle frontal gyrus; medial oFG, medial orbital frontal gyrus; medial FG, medial frontal gyrus; smFG, superior medial frontal gyrus; aCC, anterior cingulate cortex; mCC, middle cingulate cortex; pCC, posterior cingulate cortex; sTG, superior temporal gyrus; mTG, middle temporal gyrus; iTG, inferior temporal gyrus; mOG, middle occipital gyrus; Hippo, hippocampal gyrus; L, left; R, right.

and the correlation analysis in the combined SOC and OCD group showed that the rsFC between the DMN and the SN correlated positively with Y-BOCS compulsive behavior subscale scores, together with the rsFC within the DMN correlating negatively with Y-BOCS compulsive behavior subscale scores, may reflect the complicated interaction of SCZ and OCD symptoms on brain function in patients with SOC.

Concerning the relationship between the subregions of the DMN and the ECN, we found that compared with HCs, patients with SOC exhibited increased rsFC between DMN subregions and the itFG, which was similar to the SCZ and OCD group. The ECN is responsible for planning, decision-making, working memory, goal-directed behavior, and cognitive control.[28] The increased interaction between the DMN and the ECN may be related to disorganization in performing social emotion-related tasks,[79] blurred boundaries between perceptions arising from imagined scenarios and those from the external world,[39,80] imbalanced homeostasis,[81] and uncontrolled behavioral performance,[40] associated with both SCZ and OCD symptoms.[82,83]

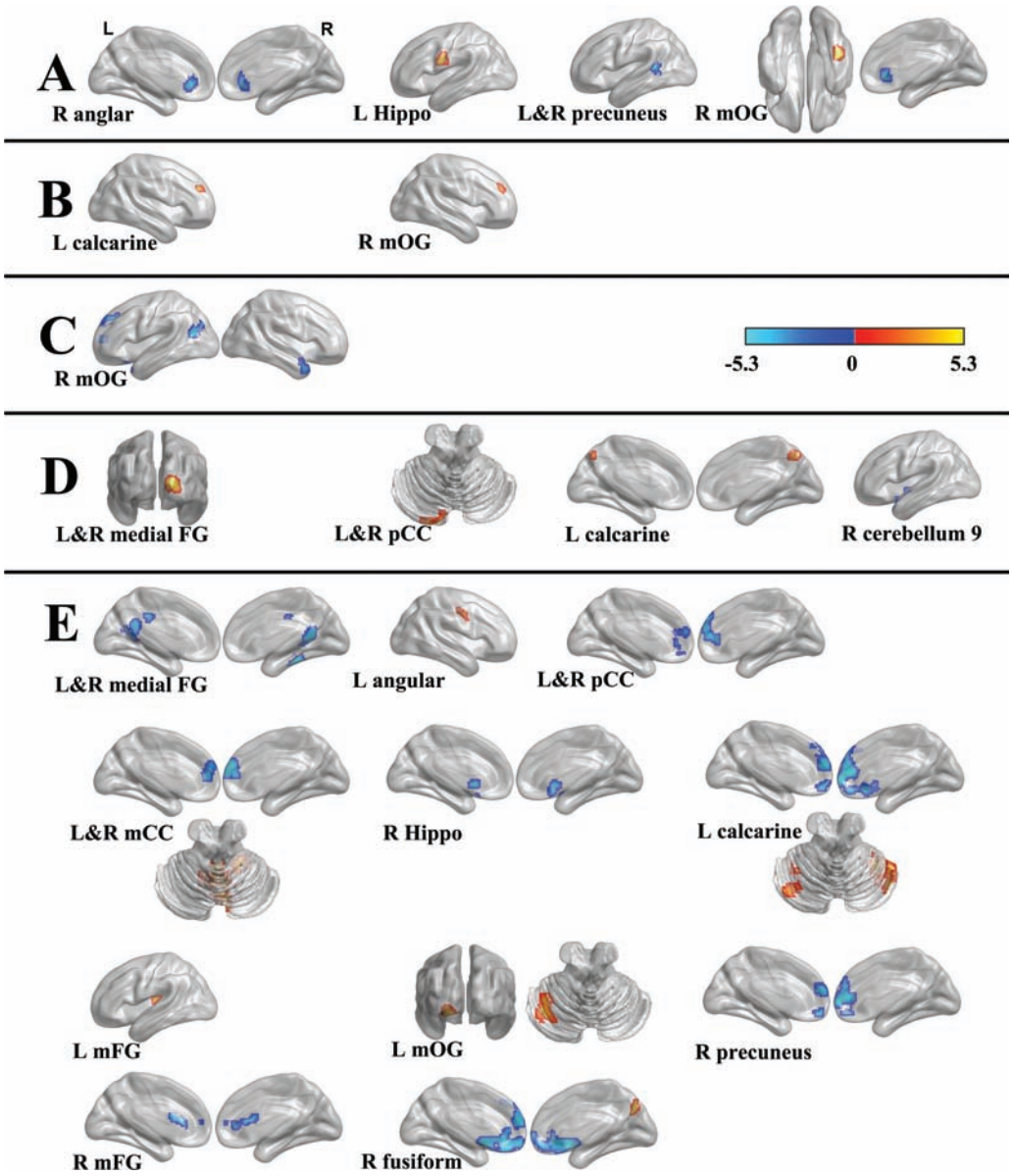

Fig. 2. Notable correlation between the subscale scores of the PANSS and whole brain rsFC of DMN subregions (as seen at the lower left sub-graph) in the combined SOC and SCZ group, between the subscale scores of the Y-BOCS and whole brain rsFC of DMN subregions in the combined SOC and OCD group ($P < .001$, cluster size > 41 voxels). (A) PANSS positive scores (combined SOC and SCZ group). (B) PANSS negative scores (combined SOC and SCZ group). (C) PANSS general scores (combined SOC and SCZ group). (D) Y-BOCS obsessive thinking scores (combined SOC and OCD group). (E) Y-BOCS compulsive behavior scores (combined SOC and OCD group). SOC, schizo-obsessive comorbidity; OCD, obsessive compulsive disorder; SCZ, schizophrenia; HCs, healthy controls; rsFC, resting-state functional connectivity; DMN, default mode network; medial FG, medial frontal gyrus; mFG, middle frontal gyrus; mOG, middle occipital gyrus; Hippo, hippocampal gyrus; mCC, middle cingulate cortex; pCC, posterior cingulate cortex.

In addition, compared with HCs, patients with SOC also showed significantly increased rsFC between DMN subregions and the mTG, which is similar to SCZ patients, but different from OCD patients. This may be a reflection of aberrant information transition between these brain regions, which may be associated with misinterpretation of auditory signals as arising from the auditory cortex without an external stimulus.[84] Previous studies in patients with SCZ have reported that hallucinations may be associated with a dysfunctional temporal gyrus.[85] It could also be related to confusion of subjective feelings and bodily sensations[45,86] and other positive symptoms.[43]

This study has several limitations. Firstly, the sample size for each group was small and our results require further verification with a larger sample. Secondly, many patients in this study were medicated, but due to the use of different antipsychotics and anti-OCD medications, we could not reliably calculate the equivalent dosages for co-variation in the statistical analysis. Thirdly, we could not exclude the possibility that brain dysfunction

elsewhere contributed to the observed clinical changes in our patients. The inclusion of additional nodes in future studies could address this issue. Fourthly, one recent study indicated that regions contributing to the DMN are spatially variable across individuals.[87] Exploring individual differences in brain network is an important research direction. Fifthly, resting state fMRI has poor temporal resolution, and the connectome needs to be validated by other structural imaging findings such as the white matter fiber tracts. These deficiencies could be resolved by advanced research methods and instruments in the future. Moreover, the rsFC results were not associated with cognitive findings (eg, working memory). Hence, no pro-cognitive effects were in fact supported by the present study. Future study needs to take this into consideration. Finally, enhanced brain dopaminergic neurotransmission has been proposed to be the crucial mechanism underlying SCZ.[88] Using transcranial direct current stimulation to affect specific dopaminergic systems to alleviate psychotic symptoms is a possible research direction.

Taken together, the present findings suggest that patients with SOC exhibit unique changes in rsFC at the DMN compared with patients with SCZ or OCD alone. These findings highlight the characteristic DMN-related rsFC changes in patients with SOC and provide new neurobiological evidence of a possible obsessive-compulsive dimension of SCZ.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub; 2013.
2. Barch DM, Bustillo J, Gaebel W, et al. Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: relevance to DSM-5. *Schizophr Res*. 2013;150:15–20.
3. Rodríguez-Testal JF, Senín-Calderón C, Perona-Garcelán S. From DSM-IV-TR to DSM-5: analysis of some changes. *Int J Clin Health Psychol.* 2014;14:221–231.
4. Keshavan MS. Nosology of psychoses in DSM-5: inches ahead but miles to go. *Schizophr Res*. 2013;150:40–41.
5. Chue P, Lalonde JK. Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. *Neuropsychiatr Dis Treat*. 2014;10:777–789.
6. Gabbay V, Johnson AR, Alonso CM, Evans LK, Babb JS, Klein RG. Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. *J Child Adolesc Psychopharmacol*. 2015;25:194–200.
7. Sheldrick RC, Benneyan JC, Kiss IG, Briggs-Gowan MJ, Copeland W, Carter AS. Thresholds and accuracy in screening tools for early detection of psychopathology. *J Child Psychol Psychiatry*. 2015;56:936–948.
8. Attademo L, Bernardini F, Quartesan R. Schizo-obsessive disorder: a brief report of neuroimaging findings. *Psychopathology*. 2016;49:1–4.
9. Zohar J. Is there room for a new diagnostic subtype—the schizo-obsessive subtype? *CNS spectrums.* 1997;2:49–50.
10. Juven-Wetzler A, Fostick L, Cwikel-Hamzany S, Balaban E, Zohar J. Treatment with ziprasidone for schizophrenia patients with OCD. *Eur Neuropsychopharmacol*. 2014;24:1454–1462.
11. Radhu N, Garcia Dominguez L, Farzan F, et al. Evidence for inhibitory deficits in the prefrontal cortex in schizophrenia. *Brain*. 2015;138:483–497.
12. Schirmbeck F, Rausch F, Englisch S, et al. Stable cognitive deficits in schizophrenia patients with comorbid obsessive-compulsive symptoms: a 12-month longitudinal study. *Schizophr Bull*. 2013;39:1261–1271.
13. Tonna M, Ottoni R, Affaticati A, et al. The impact of obsessive dimension on symptoms and functioning in schizophrenia. *Psychiatry Res*. 2015;230:581–584.
14. Esslinger C, Englisch S, Meyer-Lindenberg A, Zink M. Increased orbitofrontal cortex activation associated with" pro-obsessive" antipsychotic treatment in patients with schizophrenia. *J Psychiatry Neurosci.* 2015;40:89.
15. Owashi T, Ota A, Otsubo T, Susa Y, Kamijima K. Obsessive-compulsive disorder and obsessive-compulsive symptoms in Japanese inpatients with chronic schizophrenia—a possible schizophrenic subtype. *Psychiatry Res*. 2010;179:241–246.
16. Faragian S, Fuchs C, Pashinian A, Weizman R, Weizman A, Poyurovsky M. Age-of-onset of schizophrenic and obsessive-compulsive symptoms in patients with schizo-obsessive disorder. *Psychiatry Res*. 2012;197:19–22.
17. Tonna M, Ottoni R, Paglia F, Ossola P, De Panfilis C, Marchesi C. Obsessive-compulsive symptoms interact with disorganization in influencing social functioning in schizophrenia. *Schizophr Res*. 2016;171:35–41.
18. Lee KJ, Shin YW, Wee H, Kim YY, Kwon JS. Gray matter volume reduction in obsessive–compulsive disorder with

schizotypal personality trait. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:1146–1149.
19. Aoyama F, Iida J, Inoue M, et al. Brain imaging in childhood- and adolescence-onset schizophrenia associated with obsessive-compulsive symptoms. *Acta Psychiatr Scand*. 2000;102:32–37.
20. Iida J, Matumura K, Aoyama F, Iwasaka H, Hirao F, Sakiyama S. Cerebral MRI findings in childhood-onset schizophrenia, comparison of patients with prodromal obsessive-compulsive symptoms and those without symptoms. *Recent Prog Child Adolesc Psychiatry.* 1998;2:75–83.
21. Cunill R, Huerta-Ramos E, Castells X. The effect of obsessive-compulsive symptomatology on executive functions in schizophrenia: a systematic review and meta-analysis. *Psychiatry Res*. 2013;210:21–28.
22. Tibbo P, Warneke L. Obsessive-compulsive disorder in schizophrenia: epidemiologic and biologic overlap. *J Psychiatry Neurosci*. 1999;24:15–24.
23. Poyurovsky M, Zohar J, Glick I, et al. Obsessive-compulsive symptoms in schizophrenia: implications for future psychiatric classifications. *Compr Psychiatry*. 2012;53:480–483.
24. Sevincok L, Akoglu A, Arslantas H. Schizo-obsessive and obsessive-compulsive disorder: comparison of clinical characteristics and neurological soft signs. *Psychiatry Res*. 2006;145:241–248.
25. Calhoun VD, Eichele T, Pearlson G. Functional brain networks in schizophrenia: a review. *Front Hum Neurosci*. 2009;3:17.
26. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci*. 1995;3:89–97.
27. Schmidt A, Diwadkar VA, Smieskova R, et al. Approaching a network connectivity-driven classification of the psychosis continuum: a selective review and suggestions for future research. *Front Hum Neurosci*. 2014;8:1047.
28. Littow H, Huossa V, Karjalainen S, et al. Aberrant functional connectivity in the default mode and central executive networks in subjects with schizophrenia—a whole-brain resting-state ICA study. *Front Psychiatry*. 2015;6:26.
29. Stern ER, Fitzgerald KD, Welsh RC, Abelson JL, Taylor SF. Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PLoS One*. 2012;7:e36356.
30. Abbott AE, Nair A, Keown CL, et al. Patterns of atypical functional connectivity and behavioral links in autism differ between default, salience, and executive networks. *Cereb Cortex*. 2016;26:4034–4045.
31. Rabany L, Brocke S, Calhoun VD, et al. Default mode network functional connectivity similarities in schizophrenia and autism spectrum disorder. *Biol Psychiatry.* 2017;81:S254.
32. Penner J, Ford KA, Taylor R, et al. Medial prefrontal and anterior insular connectivity in early schizophrenia and major depressive disorder: a resting functional MRI evaluation of large-scale brain network models. *Front Hum Neurosci*. 2016;10:132.
33. Sambataro F, Wolf ND, Pennuto M, Vasic N, Wolf RC. Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. *Psychol Med*. 2014;44:2041–2051.
34. Akiki T, Averill C, Wrocklage K, et al. The default mode network in posttraumatic stress disorder (PTSD): a data-driven multimodal approach. *Biol Psychiatry.* 2017;81:S235.
35. King A, Angstadt M, Sripada C, Liberzon I. Increased default mode network (DMN) connectivity with attention networks with a mindfulness-based intervention for PTSD: seed and whole brain connectomics analyses. *Biol Psychiatry.* 2017;81:S43–S44.
36. Gilbert SJ, Dumontheil I, Simons JS, Frith CD, Burgess PW. Comment on "Wandering minds: the default network and stimulus-independent thought". *Science*. 2007;317:43.
37. Buckner RL, Carroll DC. Self-projection and the brain. *Trends Cogn Sci*. 2007;11:49–57.
38. Hahn B, Ross TJ, Stein EA. Cingulate activation increases dynamically with response speed under stimulus unpredictability. *Cereb Cortex*. 2007;17:1664–1671.
39. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1–38.
40. McKiernan KA, D'Angelo BR, Kaufman JN, Binder JR. Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage*. 2006;29:1185–1191.
41. Gong Q, Hu X, Pettersson-Yeo W, et al. Network-level dysconnectivity in drug-naïve first-episode psychosis: dissociating transdiagnostic and diagnosis-specific alterations. *Neuropsychopharmacology.* 2016;42:933–940.
42. Liu H, Kaneko Y, Ouyang X, et al. Schizophrenic patients and their unaffected siblings share increased resting-state connectivity in the task-negative network but not its anticorrelated task-positive network. *Schizophr Bull.* 2010;38:285–294.
43. Tang J, Liao Y, Song M, et al. Aberrant default mode functional connectivity in early onset schizophrenia. *PLoS One*. 2013;8:e71061.
44. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci U S A*. 2009;106:1279–1284.
45. Zhou Y, Liang M, Tian L, et al. Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophr Res*. 2007;97:194–205.
46. Orliac F, Naveau M, Joliot M, et al. Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. *Schizophr Res*. 2013;148:74–80.
47. Jang JH, Kim JH, Jung WH, et al. Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive-compulsive disorder. *Neurosci Lett*. 2010;474:158–162.
48. Markarian Y, Larson MJ, Aldea MA, et al. Multiple pathways to functional impairment in obsessive-compulsive disorder. *Clin Psychol Rev*. 2010;30:78–88.
49. Peng Z, Shi F, Shi C, Yang Q, Chan RC, Shen D. Disrupted cortical network as a vulnerability marker for obsessive-compulsive disorder. *Brain Struct Funct*. 2014;219:1801–1812.
50. Peng ZW, Xu T, He QH, et al. Default network connectivity as a vulnerability marker for obsessive compulsive disorder. *Psychol Med*. 2014;44:1475–1484.
51. Salvador R, Sarró S, Gomar JJ, et al. Overall brain connectivity maps show cortico-subcortical abnormalities in schizophrenia. *Hum Brain Mapp*. 2010;31:2003–2014.
52. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York: New York State Psychiatric Institute; 1995.
53. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
54. Goodman WK, Price LH, Rasmussen SA, et al. The yale-brown obsessive compulsive scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006–1011.
55. Gong Y. *Manual of Wechsler Adult Intelligence Scale-Chinese Version*. Changsha: Chinese Map; 1992.

56. Chao-Gan Y, Yu-Feng Z. DPARSF: a MATLAB toolbox for "Pipeline" data analysis of resting-state fMRI. *Front Syst Neurosci*. 2010;4:13.
57. Wang Y, Zou Z, Song H, et al. Altered gray matter volume and white matter integrity in college students with mobile phone dependence. *Front Psychol.* 2016;7.
58. Nalci A, Rao BD, Liu TT. Global signal regression acts as a temporal downweighting process in resting-state fMRI. *Neuroimage*. 2017;152:602–618.
59. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magn Reson Med*. 1996;35:346–355.
60. Yan CG, Cheung B, Kelly C, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage*. 2013;76:183–201.
61. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*. 2012;59:2142–2154.
62. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex*. 2012;22:158–165.
63. Biswal BB, Mennes M, Zuo X-N, et al. Toward discovery science of human brain function. *Proc Natl Acad Sci U S A*. 2010;107:4734–4739.
64. Krmpotich TD, Tregellas JR, Thompson LL, Banich MT, Klenk AM, Tanabe JL. Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. *Drug Alcohol Depend*. 2013;129:1–7.
65. Xia M, Wang J, He Y. BrainNet viewer: a network visualization tool for human brain connectomics. *PLoS One*. 2013;8:e68910.
66. Song XW, Dong ZY, Long XY, et al. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS One*. 2011;6:e25031.
67. Bluhm RL, Miller J, Lanius RA, et al. Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. *Schizophr Bull*. 2007;33:1004–1012.
68. Corcoran R, Frith CD. Autobiographical memory and theory of mind: evidence of a relationship in schizophrenia. *Psychol Med*. 2003;33:897–905.
69. Nenadic I, Maitra R, Langbein K, et al. Brain structure in schizophrenia vs. psychotic bipolar I disorder: a VBM study. *Schizophr Res*. 2015;165:212–219.
70. Minagar A, Barnett MH, Benedict RH, et al. The thalamus and multiple sclerosis: modern views on pathologic, imaging, and clinical aspects. *Neurology*. 2013;80:210–219.
71. Tuchscherer V, Seidenberg M, Pulsipher D, Lancaster M, Guidotti L, Hermann B. Extrahippocampal integrity in temporal lobe epilepsy and cognition: thalamus and executive functioning. *Epilepsy Behav*. 2010;17:478–482.
72. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006;129:564–583.
73. Wang HL, Rau CL, Li YM, Chen YP, Yu R. Disrupted thalamic resting-state functional networks in schizophrenia. *Front Behav Neurosci*. 2015;9:45.
74. Yin Y, Jin C, Hu X, et al. Altered resting-state functional connectivity of thalamus in earthquake-induced posttraumatic stress disorder: a functional magnetic resonance imaging study. *Brain Res*. 2011;1411:98–107.
75. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci Biobehav Rev*. 2005;29:399–419.
76. Kraguljac NV, White DM, Hadley N, et al. Aberrant hippocampal connectivity in unmedicated patients with schizophrenia and effects of antipsychotic medication: a longitudinal resting state functional MRI study. *Schizophr Bull*. 2016;42:1046–1055.
77. Nakao T, Okada K, Kanba S. Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. *Psychiatry Clin Neurosci*. 2014;68:587–605.
78. Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *J Psychiatry Neurosci.* 2012;37:17.
79. Noonan KA, Jefferies E, Visser M, Lambon Ralph MA. Going beyond inferior prefrontal involvement in semantic control: evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. *J Cogn Neurosci*. 2013;25:1824–1850.
80. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD. A method for functional network connectivity among spatially independent resting-state components in schizophrenia. *Neuroimage*. 2008;39:1666–1681.
81. De Haan L, Schirmbeck F, Zink M. *Obsessive-Compulsive Symptoms in Schizophrenia*. Cham, Swizerland: Springer; 2015.
82. Abramovitch A, Abramowitz JS, Mittelman A. The neuropsychology of adult obsessive-compulsive disorder: a meta-analysis. *Clin Psychol Rev*. 2013;33:1163–1171.
83. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160:13–23.
84. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. *Biol Psychiatry*. 2008;64:81–88.
85. van Tol MJ, van der Meer L, Bruggeman R, Modinos G, Knegtering H, Aleman A. Voxel-based gray and white matter morphometry correlates of hallucinations in schizophrenia: the superior temporal gyrus does not stand alone. *Neuroimage Clin*. 2014;4:249–257.
86. Aust S, Härtwig EA, Koelsch S, Heekeren HR, Heuser I, Bajbouj M. How emotional abilities modulate the influence of early life stress on hippocampal functioning. *Soc Cogn Affect Neurosci.* 2014:1038–1045.
87. Braga RM, Buckner RL. Parallel interdigitated distributed networks within the individual estimated by intrinsic functional connectivity. *Neuron.* 2017;95:457–471.
88. Hasan A, Nitsche MA, Rein B, et al. Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by transcranial direct current stimulation. *Behav Brain Res*. 2011;224:15–22.